Imaging in Osteoarthritis Clinical Trials: Metrics and endpoints Medical Imaging

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Agenda

- Uses of Medical Imaging
- Imaging Requirements
  - The metrics of measurements
- Conclusions
Uses of Medical Imaging

• *Diagnosis*

• *Prognosis*

• *Monitoring therapy*

• *Monitoring Natural History of Disease*
Imaging Requirements

- **Diagnostic Sensitivity**
- **Precision/Accuracy**
- **Reliability**
- **Relevance**
- **Cost effective**
- **Acceptance by regulatory agencies**
- **Acceptability to Subject**
- **Safety to subject and operator**

Bone density measurements in clinical trials: the challenge of ensuring optimal data; Miller CG, Br. J Clin Res. 1993 Vol. 4, p. 113-120
Diagnostic Sensitivity
Normal - Abnormal Difference

<table>
<thead>
<tr>
<th>Normal</th>
<th>Diseased</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Normal</th>
<th>Elderly</th>
<th>Diseased</th>
</tr>
</thead>
</table>
ROC Analysis

- **Sensitivity** - True Positive
- **Specificity** – False positive

<table>
<thead>
<tr>
<th>Predicted Outcome</th>
<th>Actual Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>True +ve</td>
<td>False +ve</td>
</tr>
<tr>
<td>False -ve</td>
<td>True -ve</td>
</tr>
</tbody>
</table>
Imaging Requirements

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• *Precision/Accuracy*
• *Reliability*
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Accuracy

Standard error of the estimate of linear regression between actual and measured parameter

i.e., when correctly calibrated, the measured result is close to the actual value
**Precision**

Standard deviation of the difference between pairs of repeat measurements, usually expressed as a percentage of the average value (coefficient of variation), i.e., the reproducibility of the measurement. When repeating a measurement of the same object under the same circumstances, how similar are the results?
Precision

Measured as coefficient of variation:

\[ \%C.V. = \frac{S.D.}{\text{Mean}} \]

Standardized Coefficient of Variation:

\[ \text{S.C.V.} = \frac{S.D.}{\text{Mean}} \times \frac{\text{Mean}}{\text{Normal Range}} = \frac{S.D.}{\text{Normal Range}} \]

NB: Normal range = 5%-95%

MillerCG et al Osteo Int 1993
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One Problem – Calibration drift
Reliability – Site Selection

• Subject recruitment

• Imaging Modalities
  – X-ray – How to standardize?
  – MRI 1.5T or 3.0T?

• Trained technologists?
  • Open to being trained?
  • Accept trial standard – not local site standard?

• Imaging Guidelines
Reliability – Image QC

• **Training**
  – Sites – good acquisition
  – Central Readers (radiologists)

• **Administrative QC**
  – Anonymized
  – Right subject, right time point?

• **Image QC**
  – Correct anatomical coverage?
  – Motion artifacts?
  – Acquired according to Imaging Guidelines?

• **Up to 30% of all images will be poor quality or unusable without Image QC**
Reader Reliability

• Qualified Radiologists

• Reader training on the read scoring system
  – EG KL or Modified KL (at least 10 versions)
  – How to score WORMS, BLOKS, MOCART etc

• Inter-reader calibration
  – Eligibility
  – Efficacy/Safety

• Inter and intra Reader calibration
  – on going?
Reliability – Computer systems

• Validation

• CFR 21 Part II compliance
  – Image Management systems
  – Read systems

• Meets new FDA draft Guidance for Industry:
  – Guidance for Industry: Standards for Clinical Trial Imaging Endpoints (Aug 2011)
  – EG Charter, monitors, phantoms, QC etc
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Gold Standard?  Or Best method?

Do either have any clinical meaning or relevance?
Validation

• Validation as a BioMarker/Surrogate
• Does this match the requirements for a biomarker/surrogate end point?
• Is it on the correct biological pathway?
Validation

• Validation as a BioMarker/Surrogate
• Does this match the requirements for a biomarker/surrogate end point?
• Is it on the correct biological pathway?
BioMarker Definitions

“A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, pharmacologic, or clinical significance of the results.”

A probable valid biomarker is defined as

“a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is a scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, pharmacologic, or clinical significance of the test results.”
Validation

• Validation as a BioMarker/Surrogate
• *Does this match the requirements for a biomarker/surrogate end point?*
• *Is it on the correct biological pathway?*
Reasons for Surrogate Failure: 1

Reason for failure of surrogate end point: The surrogate is not in the causal pathway of the disease process.
Reasons for Surrogate Failure: 2

Reason for failure of surrogate end point:
Of several causal pathways of disease, the intervention affects only the pathway mediated through the surrogate.
Reason for failure of surrogate end point: The surrogate is not in the pathway of the intervention’s effect or is insensitive to its effect.
Reasons for Surrogate Failure: 4

Reason for failure of surrogate end point:
The intervention has mechanisms of action independent of the disease process.
Dotted lines = mechanisms of action that might exist.

Reasons for Surrogate Success:

The setting that provides the greatest potential for the surrogate end point to be valid.

Fleming TR, DeMets DL. Surrogate End Points in Clinical Trials: Are We Being Misled? Annals of Int Med; 125; 605-613, 1996;125:605-613
Imaging Requirements

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- Cost effective
- Acceptance by regulatory agencies
- Patient acceptability
- Safety to patient and operator
Cost Effective

Varies with study phase

• Phase I/II - Not relevant
• Phase III
• Phase IIIb
• Phase IV and clinical setting
Imaging Requirements

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Acceptable to Regulatory Agencies

• For general use
• For special use cases
• Supporting data in clinical trial submissions

E.G. MRI is an accepted clinical endpoint, but NOT clinical trial end point
FDA Directives

• March 1997
  • Guidance states that a single, multi-endpoint trial may be used in lieu of several separate trials. Example: Betaseron

• October 1998
  • Draft Guidance for Industry - Developing Medical Imaging Drugs and Biologics.

• June 2004
  • Guidance for industry Developing Medical Imaging Drug and Biological Products, Part 1, Part 2, Part 3.

• October 2011
  – Draft Guidance for Industry on Standards for Clinical Trial Imaging Endpoints

• Expected final Oct/Nov 2012
  • http://www.regulations.gov/#!searchResults;rpp=10;po=0;s=FDA%25E2%2580%25932011%25E2%2580%2593D%25E2%2580%25930586
Regulatory Issues

• Image data will be treated with the rigor as other clinical data
  • Loss of data viewed seriously
  • 95% image data submission is possible

• Site Image Acquisition

• Efficacy Assessment
  • Independent
  • Central
  • Blinded Readings

• End point data should match the protocol end point (not always the case!)
Regulatory Issues

• **Standardized Reading Process**
  - Identical Hardware/Software
  - Same image display order of randomized images
  - Allow for 100% duplication of reading process

• **Optimum Method to Display Images**
  - Digital Images
  - Electronic control of data retrieval
  - Digital measurements
  - Reproduce image display order
  - Review response assessments
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Subject Acceptability

- Is it comfortable?
- Is it frightening?
- Is it a +ve experience?
  - EG MRI – Claustrophobia
- How does the technologist treat the subject?
- Will the subject return for follow-up?
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Safe for the Subject

Variable levels of risk depending on

- Phase of study
- Disease
- Phase of the disease
Safety for the Operator
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cindunistat Results: OARSI 2012

A6171016: LS-Mean (95% CI) Change from Baseline in Joint Space Width
Subjects with Kellgen and Lawrence Grade <= 2

LS-Mean (95% CI) Change from Baseline in Joint Space Width

Placebo
SD-6010 50 mg QD
SD-6010 200 mg QD

Weeks
BL 48 96

*
Failure – Why?

• Calcitonin failed on JSN Endpoint
• Failed Futility Analysis (placebo did not demonstrate significant change)
• 2 Possible reasons:
  – Incorrect subject enrollment (poor KL scoring)
  – Poor QC of images so precision was decreased
  – Combination of both
Conclusion: Where to next?

- Diagnostic Sensitivity
- Precision/Accuracy
- Reliability
- Relevance
- Cost effective
- Acceptance by regulatory agencies - DRIVER
- Acceptable to Subject
- Safety to subject and operator
Conclusion

• Are we using the best surrogate?

• Are we evaluating OA correctly?
  – What is the pathophysiology?
  – Should we sub categorize?

• New Guidance Documents
  – Validation of Biomarkers
  – Standards for Clinical Trial Imaging End Points

• Evaluate new BioMarkers Carefully
  – Maximize the metrics!